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Letter to the Editor

Does concomitant administration of sevelamer hydrochloride and lanthanum carbonate modify the control of phosphatemia?

Dear Editor,

Hyperphosphatemia is a common complication in patients with chronic kidney disease stage 5 on hemodialysis. Although dialysis and dietary restrictions are capable of reducing serum phosphate to a limited extent, the majority of patients will require additional treatment with phosphate binders to reduce serum phosphate concentration to the target range of 3.5-5.5 mg/dl, as recommended in the 2003 Kidney Disease Outcomes Quality (KDOQY) guidelines[1].

In clinical practice is not uncommon the co-administration of different types of phosphorus binders especially in patients with poor response to one component, where we try to achieve greater efficiency with reduced doses of each. Our aim was to determine whether serum phosphate varied when sevelamer hydrochloride and lanthanum carbonate were administrated concomitantly in comparison to administration at separate meals.

Patients already requiring both sevelamer hydrochloride and lanthanum carbonate for serum phosphate control and undergoing thrice-weekly hemodialysis treatments at our center were recruited. We excluded patients who had been on hemodialysis for less than three months, had had a parathyroidectomy in the last three months, intact parathyroid hormone (iPTH) >550 pg/ml, hyperphosphatemia (> 6.5 mg/dl) or hypophosphatemia (< 3.5 mg/dl) before dialysis, severe hypercalcemia (Ca > 10.5 mg/dl) before dialysis, clinical significant gastroparesis, malabsorption, or any other condition that could interfere with administration of drugs. 14 patients were eligible for our study (Table I). Treatment with cinacalcet hydrochloride, vitamin D or compounds containing phosphorus, magnesium, aluminum or calcium (as phosphate binders) was not permitted during the study. The local Ethics Committee approved the study design and all subjects provided informed consent. We conducted a crossover randomized study in which each subject, underwent three 4-week study periods (Figure 1). There was a two-weeks washout period before each study period. The dose of phosphate binding agents in our study had been determined for each patient according to their pre-study dose. Hence, there was no titration after the wash-out periods, and patients were immediately started on their pre-study total daily dose of chelators. The mean daily dose of phosphate binders was 4.800 ± 800 mg/day of sevelamer hydrochloride (Renagel®) and 3.000 ± 750 mg/day of lanthanum carbonate (Foznol®). For period 1 and 2, patients received one of the two study medications. Patients were instructed to take these drugs with their meals, as usual. During the period 3, both chelators were administered together at each meal at half dose of the period 1 or 2. During the study periods, patients were instructed to keep their usual eating habits constant.

The primary outcome was the difference between serum phosphate measured before dialysis, at the end of period 1 and the period 2 ("separate" period) and at the end of period 3 ("concomitant" phase). Secondary outcomes were the differences between serum calcium, intact parathyroid hormone, albumin, total cholesterol, LDL, HDL, triglycerides, arterious pH and

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Table I. Demographic and baseline characteristics of the patients (N = 14).

Patient characteristics		
Median age in years	60 (48-78)	
Gender: male	7 (50%)	
Mean duration of dialysis (years)	5.1 (3.1)	
Median body mass index (Kg^2/m^2)	24 (10-29)	
Diabetes	5 (36%)	
Hypertension	8 (62.5%)	
Primitive kidney disease:	Nephroangiosclerosis	6 (43%)
	Glomerulonephritis IgA	1 (7%)
	Diabetic nephropathy	4 (28%)
	Policistic	1 (7%)
	Unknown	3 (21%)
Pre-dialysis phosphate-binders used:	Carbonate calcium	2 (14%)
	Sevelamer hydrochloride	7 (50%)
	Lanthanum carbonate	5 (36%)
Use of vitamin D analogs before the study:		5 (35%)

serum bicarbonate. We used ANOVA to test for differences between periods. Laboratory values were obtained at baseline and at monthly intervals. An alpha level of 0.05 was considered statistically significant. We report the means and 95% confidence intervals of the differences. Baseline characteristics of the patients at enrolment in the study are listed in Table I. The duration of dialysis was 4 hours for all patients. All were dialyzed with high-flux filters. Dialysis parameters were kept constant during the whole study. The results for primary and secondary outcomes are shown in Table II. The baseline serum phosphorus level (mean ± SD) of the patients was 7.0 ± 1.2 mg/dl. At the end of the study the mean serum phosphorus of SH group was 4.5 ± 0.7 mg/dl ($p < 0.05$); in LC group was 4.10 ± 0.7 mg/dl ($p < 0.05$). When administered together, the mean serum phosphorus was 4.60 ± 0.8 mg/dl ($p < 0.05$) (Figure 2). A reduction of serum phosphate levels was successfully maintained for all three study periods. In

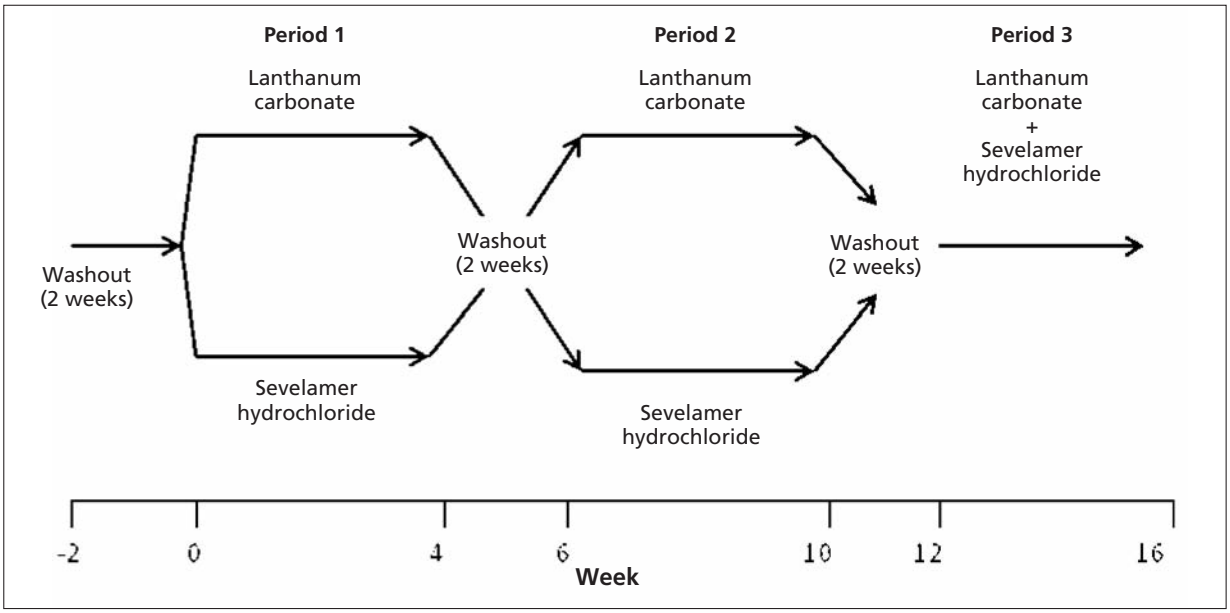

Figure 1. Study design. At the start, following washout, patients were randomized to receive either lanthanum carbonate or sevelamer hydrochloride. Following a 4 weeks' treatment, patients underwent a second washout period and switched to the alternative binder for 4 weeks. After this period patients underwent to a third washout and then they passed to the final period 3 in which they received lanthanum carbonate plus sevelamer hydrochloride.

Table II. Results at the end of the three study periods.

	Before the study	SH	LC	SH+LC
P (mg/dl)	7.0 ± 1.2	4.5 ± 0.8*	4.10 ± 0.7*	4.60 ± 0.8*
Ca (mg/dl)	9.60 ± 0.47	9.40 ± 0.30	9.10 ± 0.25	9.20 ± 0.32
iPTH (pg/ml)	254 ± 100	270 ± 80	260 ± 75	250 ± 77
Albuminemia (g/dl)	3.9 ± 0.29	4.10 ± 0.30	3.9 ± 0.60	4.20 ± 0.65
Tot. cholest. (mg/dl)	230 ± 100	185 ± 85	200 ± 90	180 ± 85
LDL (mg/dl)	107 ± 14	75 ± 15*	100 ± 20	107 ± 25
HDL (mg/dl)	38 ± 9	32 ± 7	35 ± 10	38 ± 12
Triglycer. (mg/dl)	203 ± 70	190 ± 40	195 ± 15	201 ± 35
pH	7.33 ± 0.4	7.31 ± 0.3	7.33 ± 0.4	7.37 ± 0.5
HCO_3^- (mmol/L)	16 ± 2.2	18 ± 1.2	20 ± 2.2	23 ± 2.2*
pCO_2 (mmol/L)	33 ± 1.1	34 ± 1.2	35 ± 1.3	34 ± 1.2

Values are mean ± SD; iPTH, intact parathyroid hormone. *$p < 0.05$ vs. before the study.

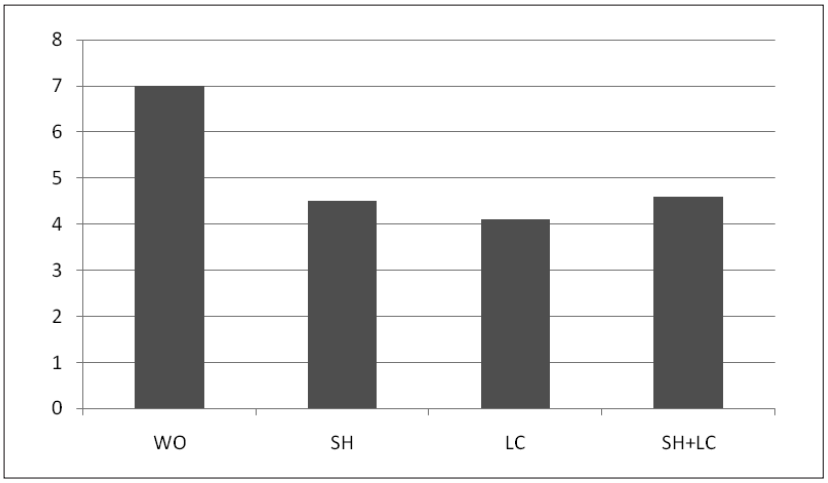

Figure 2. Mean serum phosphorus before the study (wash-out) and after treatment of sevelamer hydrochloride (SH), lanthanum carbonate (LC) and concomitant administration of SH and LC. Data are mean ± standard deviation. A significant reduction of serum phosphate was observed in all three study periods (*$p < 0.05$).

the SH group we observed a statistical significant reduction in LDL (75 ± 15 mg/dl – $p < 0.05$). In addition, we detected an increase of HCO_3^- (23 ± 2.2 – $p < 0.05$) when the two drugs are administered together. We observed no adverse events when the patients took the phosphate binders separately or concomitantly. All patients concluded the study. The primary analysis of data from this study suggests that at the single doses, sevelamer hydrochloride and lanthanum carbonate are effective phosphate binders that reduce phosphoremia to a similar degree in hemodialysis patients; we observed a 0.4 mg/dl greater reduction with LC. When the two drugs were administered together, we observed an hypophosporemic action similar to when they were taken individually, still significantly lower than the wash-out. We believe that this association is possible. Our limitation of this study is its small sample size. Further investigations are necessary in long-term studies.

References

1. National Kidney Founfation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42: S1-S201.

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